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Yellow Filter Effect on Melatonin Secretion in the Eye: Role in IOP Regulation

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ABSTRACT

Purpose: Melatonin is a neurohormone mainly synthesized in the pineal gland; however, it is also present in the aqueous humor. One of melatonins' functions in the eye is the regulation of intraocular pressure (IOP). Melatonin is known to be sensitive to light. Recently, the photopigment which controls melatonin synthesis, melanopsin, was found in the crystalline lens. Therefore, light conditions are an interesting possible way of regulating melatonin levels in the aqueous humor. The current study used yellow filters, since melanopsin is activated by short wavelength (blue light).

Methods: New Zealand white rabbits were used, divided in two groups, one under controlled 12 h light/dark cycles, while the rest had their cages encased with a yellow filter (λ 465–480). IOP measurements were taken every week at the same time before they were anesthetized for aqueous humor extraction.

Results: Keeping the rabbits under the yellow filter resulted in a decrease in IOP up to 43.8 ± 7.8% after 3 weeks. This effect was reversed after the topical application of selective and nonselective melatonin receptors antagonists, 4PPDOT and luzindole. Also, blocking melanopsin by its antagonist AA92593 under white light condition decreased IOP. Finally, melatonin levels were found significantly higher in the aqueous humor of rabbits developed under yellow filter compared to controls (37.4 ± 4.2 and 15.3 ± 3.1 ng/ml, respectively).

Conclusion: Yellow filters modulate melatonin levels in the aqueous humor due to deactivating melanopsin activity. This effect leads to a decrease in IOP mediated by melatonin receptors.

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Yellow filter; intraocular pressure; melatonin; melanopsin

Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine) is a molecule first discovered and described in the pineal gland.[1] It was classically considered to be exclusively produced by this structure until years later when melatonin synthesizing enzymes were found in several organs and structures.[2] Among the huge number of organs and cells producing melatonin, the eye was one of the first organs discovered to synthesize melatonin, first starting from the retina.[2] Afterward, the attention was attracted to several ocular structures and melatonin now is known to be synthesized in the iris, ciliary body,[3] crystalline lens,[4,5] and the lacrimal gland.[6]

In the eye, melatonin plays numerous functions. It has the ability to accelerate corneal wound healing,[7] it serves as an antioxidant in the eye, and it protects the eye against oxidative stress due to aging or diseases.[8–10] Moreover, melatonin lowers intraocular pressure (IOP) and participates in the physiology of the aqueous humor, as well as the pathophysiology of glaucoma.[11,12]

Glaucoma is a multifactorial disease which results in a progressive irreversible optic neuropathy and peripheral visual field loss.[13] It is the second leading cause of vision loss[14] and it is developed as a consequence of several risk factors, the only controllable one being IOP.[15] Glaucoma can be controlled through different drugs aiming to lower IOP. Nevertheless, apart from the commercially available compounds, more substances such as melatonin and its analogs rise as a possible therapeutic agent to lower IOP and control glaucoma.[12]

Melatonin synthesis is controlled by light–darkness cycles and this is specially relevant in the eye since it is the window of the body to the outside. Several years ago, a photo pigment named melanopsin was described in a small subclass of the retinal ganglion cells. These studies showed that it participates in a nonimage forming pathway since it was active and functional in blind subjects and, moreover, in enucleated mice.[16–18] This photo pigment is responsible for photo-entrainment, and its activation occurs by means of short wavelength light (470–480 nm) leading to melatonin suppression.[19]

Evidences during the last three decades have indicated that illumination, received by the eye, has an influence in many human physiological and behavioral aspects.[20,21] For instance, light constricts the pupil, increases heart rate, body temperature, and suppresses melatonin synthesis.[22,23] Based on these changes in the physiology carried out by light, several therapeutic applications have been developed.[24] For example, light has been shown to have antidepressant properties, specially for the treatment of seasonal effective disorder,[25,26] also, a proper timed light exposure has been developed as a therapy for circadian rhythm sleep disorders and circadian disruption due to jet lag, and finally light has been used for depression treatment.[27,28] On the other hand, short wavelength light presents some serious harm to the

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eye, since it could lead to retinal cells damage.[29,30] All these studies and discoveries highlight the importance of light and, consequently, melanopsin physiological role.

Recently, melanopsin has been described in the crystalline lens epithelium of humans. This study has shown that epithelial crystalline lens cells responded to light by modifying melatonin levels. An increment in melatonin was observed after hours of incubation in darkness, while under light conditions, the synthesis of this substance was abolished. This effect was confirmed to be regulated by melanopsin present in the lens.[31] Together with the fact that melatonin is present in the aqueous humor, due to its synthesis in the ciliary body, we believe that melatonin is also coming from neighbor tissues in contact with the aqueous humor such as the crystalline lens.

In the current work, we show how melatonin present in the aqueous humor can be modulated by means of yellow filters in New Zealand white rabbits and how the presence of this substance can modify IOP.

Material and methods

Animals

Male New Zealand white rabbits, weighing an average of 2.5 ± 0.5 kg, were used for this study. The animals were kept in individual cages with free access to food and water. The control and pharmacological groups were kept under controlled 12 h day–night cycles, while a different group was kept in cages enveloped with a yellow filter, though receiving 12 h day–night cycles. This study adhered to the ARVO Statement for the Use of Animals in Opthalmic and Vision Research, and also all animal care and experimental procedures were carried out in accordance with the European Communities Council Directive (86/609/EEC).

Experimental procedures

The effect of the yellow filter (465–480) as well as the pharmacological compounds which were tested measuring IOP were carried out using a TonoVet contact tonometer supplied by Tiolat Oy (Helsinki, Finland). All the measurements were performed at the same time of the day, 10 am, in order to minimize IOP variations. The TonoVet takes five consecutive IOP measurements and calculate the mean of the value. At any given time, IOP is measured three times and the values obtained were transformed into mean ± s.e.m. For the experiments using the yellow filter, IOP was measured once a week during 1 month before taking them out of the filter to study the possible change during the following month. For pharmacological assays, two measurements were taken at 30 min interval before any substance was added. IOP was measured at different intervals of time depending on the experiment, and the substances were applied topically (20 µl) in a bilateral way.

For the filter group, 20 µl cocktail of luzindole (nonspecific antagonist for melatonin receptors) and 4PPDOT (4-phenyl-2-propionamidotetralin, MT2 specific antagonist), both provided from Tocris, Bristol, UK, were administered as eye drops at final concentration of 100 µM. Experiments were done after 3 weeks in yellow filter-covered cages. IOP measurements were taken after 10, 30, 45, 60, 90, 120 min of instillation.

For the control group, 20 µl of AA92593 (melanopsin antagonist, prepared in PEG-400, DMSO, SML0865, Sigma, St. Louis, Mo, USA) was used at a final concentration of 100 µM. IOP measurements were done at 20 min, 40 min, 1, 2, 3, 4, 5, and 6 h after applying the antagonist.

For the aqueous humor collection, rabbits were anesthetized with a subcutaneous injection of a mixture of ketamine (7.5 mg/kg, Imalgene 1000, Merial, Barcelona, Spain) and Domitor (0.25 mg/mg, DOMTOR®, Orion Pharma, Espoo, Finland). Aqueous humor (100 µl) was extracted with a syringe connected with a 30-ga needle in the sacro-corneal limbus. Samples were stored in −20°C until the time of the analysis.

Samples of the aqueous humor were processed for HPLC (High Performance Liquid Chromatography) analysis using the protocol described elsewhere.[32] Briefly, samples were submitted to a 98°C dry bath for 2 min before they were transferred to ice during 10 min, finally, the samples were centrifuged to pellet proteins at 13,000 *g* for 10 min at 4°C before the injection. In brief, the column was a Kromaphase C18 column 5.0 mm (25 cm in length, 0.4 cm inner diameter) (Scharlau, Madrid, Spain). The system was equilibrated overnight with 40% methanol and 60% H_2O. Measurements were performed at a flow rate of 0.8 ml/min fixing the detector at a wavelength of 244 nm. The chromatographic system for all the determinations consisted of a 1515 Isocratic HPLC pump, a 2487 dual absorbance detector, and a Rheodyne injector, all managed by the software Breeze from Waters (Milford, MA). Quantification melatonin was performed by comparing the samples with the corresponding external standard provided by Sigma.

Statistical analysis

Data represent the mean ± s.e.m of separate indicated number of experiments for each case, and statistical significance was calculated by ANOVA or Student *t*-test when necessary. All the plots were obtained by GraphPad Prism (GraphPad Software Inc., San Diego, CA).

Results

Effect of yellow filter on IOP

Recently, the presence of melanopsin and its effect on ATP release have been demonstrates in New Zealand with rabbits.[33] Rabbits maintained under the yellow filter presented a significant reduction of IOP, this reduction was most appreciated after 3 weeks under the yellow filter. IOP decreased up to 43.8 ± 7.8% (***$p < 0.0001$, $n = 6$) compared to the control animals (Figure 1A). This effect was completely reversed 30 min after the topical application of both the selective and nonselective melatonin receptor antagonists, 4PPDOT and luzindole, respectively (Figure 1B). This is a clear indication of the involvement of melatonin receptors in the hypotensive effect observed by the use of this filter. When the rabbits were placed under white light/darkness cycles, it resulted in a gradual recovery of the IOP reaching values similar to the control ones after 4 weeks (Figure 1A; ***$p < 0.0001$, $n = 6$).

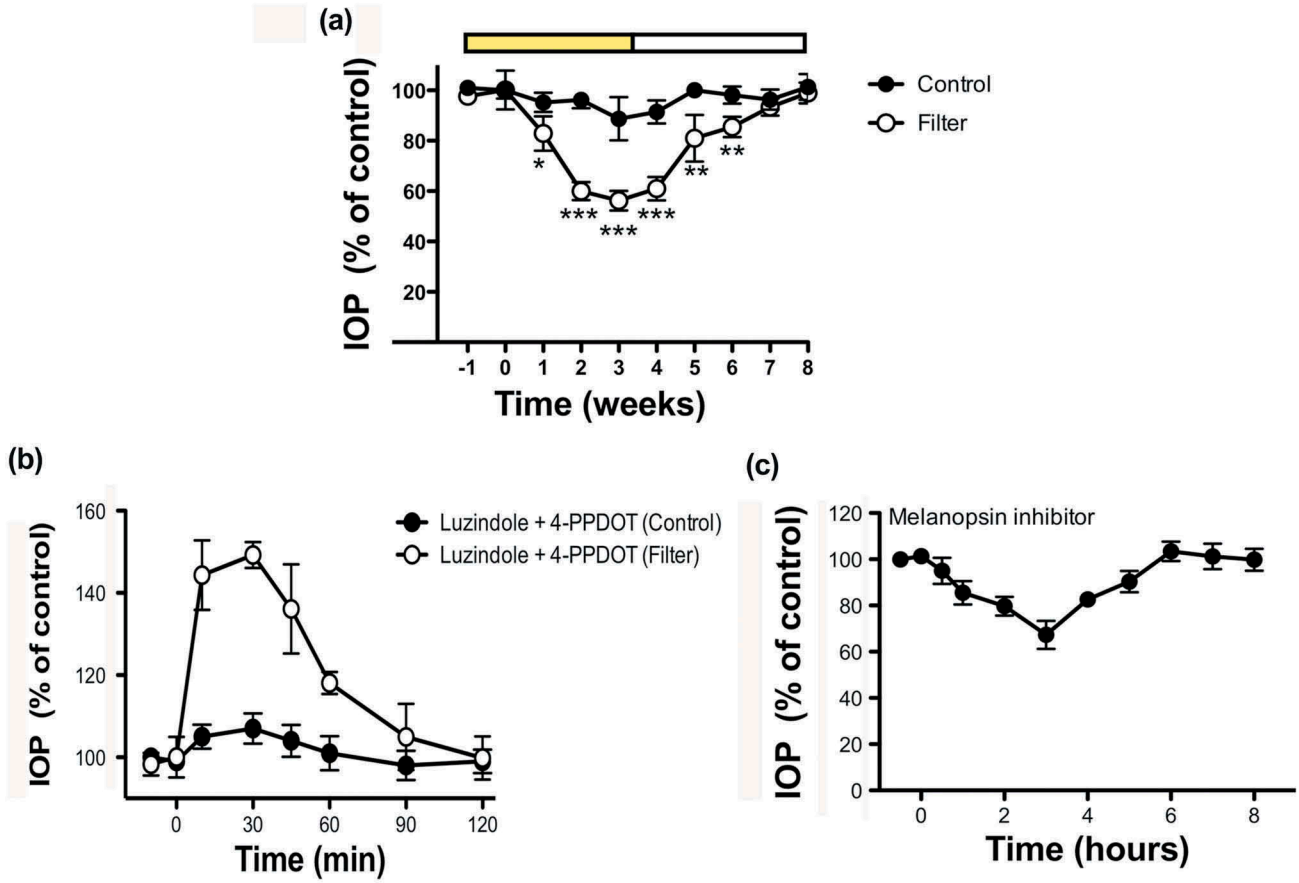

Figure 1. (A) Effect of yellow filter on rabbit intraocular pressure. Time course of yellow filter for 4 weeks followed by the recovery time in 12/12 h light darkness. Hundred percent represents the intraocular pressure before starting the experiments (i.e., at *t* 0) and was equivalent to 8.70 ± 1.30 mm Hg. Values represent the mean ± s.e.m (***$p < 0.0001$, $n = 6$) with respect to the control values. (B) Effect of the instillation of melatonin antagonists (luzindole + 4PPDOT) in rabbits after 3 weeks in yellow filter-covered cages compared to the control. This reduction of IOP due to the filter was completely reversed 30 min after the topical application of both the selective and nonselective melatonin receptor antagonists. (C) Line graph confirming the implication of melanopsin receptor in IOP. Hundred micrometer of melanopsin antagonist AA92593 resulted in a reduction of IOP after 2 h of topical instillation (***$p < 0.0001$, $n = 6$).

Involvement of melanopsin on light effect and melatonin contribution

To confirm melanopsin involvement on light effect previously described, we were able to block melanopsin by using its selective antagonist AA92593 under white light condition. Interestingly, inhibiting melanopsin under light condition resulted in a similar behavior to the one obtained by the filter. IOP dropped up to 32.7 ± 15.0% (***$p < 0.0001$, $n = 6$) 2 h after the application of a single dose of melanopsin antagonist compared to the control rabbits (Figure 1C).

A possible explanation for the changes observed on IOP was the possible increase in melatonin levels in the aqueous humor. As expected, melatonin levels have increased significantly from 16.33 ± 4.50 ng/ml (before submitting rabbits to yellow filter) to 39.04 ± 5.56 ng/ml (during the third week under the yellow filter, ***$p < 0.0001$, $n = 6$) in the aqueous humor. Control animals, those under normal white light, showed melatonin levels of 16.50 ± 2.50 ng/ml, values which did not change significantly during 8 weeks (17.14 ± 5.30 ng/ml last week of the assay) (Figure 2).

Interestingly, the increment of melatonin levels in the aqueous humor has returned to its normal values gradually when the rabbits were moved from the yellow filter to a normal white light/darkness cycle (Figure 2). They showed 16.80 ± 4.55 ng/ml of melatonin in the aqueous humor, this reduction is significant compared to the highest concentration found in the same animals after 3 weeks in the yellow filter (***$p < 0.0001$, $n = 6$).

Discussion

The current work describes for the first time the effect of blocking short wavelength light over IOP. Submitting New Zealand rabbits to a yellow filter environment resulted in a decrease of IOP observed after 2 weeks. This effect was reversed by using both, the selective and nonselective melatonin receptors antagonists, 4PPDOT and luzindole, respectively. Moreover, this indicates the role of melanopsin in regulating melatonin synthesis in the aqueous humor. From one hand, melatonin, present in the aqueous humor, was significantly higher in the rabbits under yellow filters compared to the control animals under white light. On the other hand, blocking melanopsin by means of its selective antagonist AA92593 was able to decrease IOP in rabbits living under normal light condition.

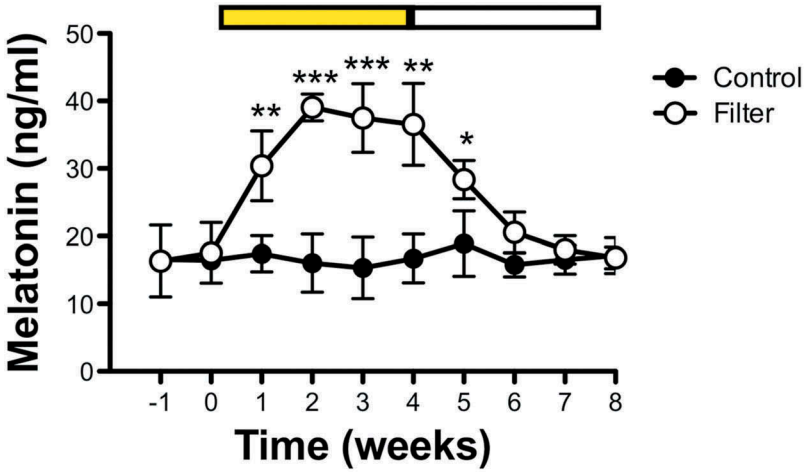

Figure 2. Presence of melatonin in the aqueous humor of New Zealand rabbits. Line graph presenting the concentrations of melatonin calculated from the chromatographic studies of controlled 12/12 light/darkness cycles compared to rabbits kept in cages enveloped with a yellow filter. Values are the mean ± s.e.m of six independent experiments (***$p < 0.001$).

These results are indicating a powerful effect of light modulating IOP values. Concerning the possible hypotensive effect of the yellow filters, a study by Ichikawa and colleagues was done to analyze changes in blood pressure and assess sleep duration in patients before and after they underwent cataract surgery and intraocular lens (IOL) implantation with yellow-tinted lenses. Interestingly, these patients had a significant decrease of cytosolic and diastolic blood pressure 1 month after implanting the yellow-tinted IOL.[34]

The ability of blocking this decrease in IOP by means of antagonizing melatonin receptors is highlighting that the hypotensive effect is due to the direct binding of melatonin to its membrane receptors. These receptors are present in several structures in contact with the aqueous humor, and in this sense, studies showed that melatonin receptor activation in the nonpigmented ciliary body epithelial cells leads to a reduction of Cl^- efflux and hence lowering the IOP.[35] This is of great importance since it could open a possible compliment way to increase efficient melatonin in the aqueous humor as a novel way of drug delivery, by augmenting its endogenous levels as previously suggested.[36]

Another melatonin producing structure in the eye is the crystalline lens, where it is bathed also in the aqueous humor.[37] A recent study discovered melanopsin presence in the lens, and its ability to regulate melatonin secretion from the epithelial lens cells.[31] Although results in that study indicated an increment of melatonin after 8 h of incubation in darkness that effect was blocked by the melanopsin antagonist. In the present work, the blockade of melanopsin by means of the antagonist AA92593 produced an increment in melatonin levels resulting in a drop of IOP. This effect could be explained by the activation of the key enzyme of melatonin synthesis, AANAT, since it can trigger melatonin production in a very quick manner.[38] Very recently, it has been possible to demonstrate that a yellow filter can modify the release of the nucleotide ATP from rabbit lenses. Interestingly, either with the whole animal or with cultured lenses, the blockade of melanopsin significantly reduced the release of ATP.[33] This is indicating that light, activating the photopigment melanopsin, can induce the release of this nucleotide. On the contrary, and as described in the present work, light inhibits the synthesis of melatonin. Although the functions of melatonin and ATP in the eye are different,[39] the possibility of modifying the presence of these substances by using a filter is something relevant. It is possible by using filters to increase the presence of melatonin and to decrease the release of ATP,[33] therefore acting pharmacologically without using drugs but by using the light as an agonist or antagonist.[40]

In summary, melanopsin photo pigment plays an indirect, still important role on IOP modulation through the regulation of melatonin production in the aqueous humor. The use of yellow filters blocking blue light could be a novel approach to reduce IOP and prevent the progression of glaucoma.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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